AEROSOLIZED RIBAVIRIN TREATMENT OF INFANTS WITH RESPIRATORY SYNCYTIAL VIRAL INFECTION

A Randomized Double-Blind Study

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Abstract We evaluated a new antiviral agent, ribavirin, in the treatment of infants hospitalized with lower-respiratory-tract disease from respiratory syncytial virus. Ribavirin or placebo was administered to 33 infants in a double-blind manner by continuous aerosol for three to six days. Seventeen infants were treated with placebo, and 16 with ribavirin. By the end of treatment, infants receiving ribavirin had significantly greater improvement in their overall score for severity of illness, in lower-respiratory-tract signs, and in arterial oxygen saturation. Viral shedding was also diminished in the treated groups as compared with the placebo group. No side effects or toxicity were associated with the aerosol therapy. Isolates of respiratory syncytial virus obtained from the infants over the course of therapy showed no change in sensitivity to ribavirin. (N Engl J Med 1983; 308:1443-7.)

RESPIRATORY syncytial virus (RSV) remains the most important respiratory pathogen of infants and young children, producing yearly outbreaks in this country.[1-4] Immunity to this virus is of short duration, and repeated infections may occur throughout life.[4,5] No treatment, prophylaxis, or vaccine has thus far been available for this disease. However, a new experimental antiviral agent has recently shown promise not only in the treatment of influenza but also in that of RSV infection.[6-8] Ribavirin (1-β-D-ribofuranosyl-1,2,4,-triazole-3-carboxamide) is a synthetic nucleoside that possesses antiviral properties in vitro against a variety of both RNA and DNA viruses.[9-11] The course of both influenza A and influenza B infections in adults has been shown to be ameliorated by ribavirin therapy, especially when this agent is administered by small-particle aerosol.[6,7,12-14] Subsequently, the effects of ribavirin on RSV infection were assessed. Antiviral properties against RSV were first demonstrated in vitro and in a cotton-rat model.[15,16] More recently, the effect of ribavirin given by small-particle aerosol on experimental RSV infection in young adults has been evaluated.[8] Volunteers treated with ribavirin appeared to have diminished systemic symptoms, fever, and viral shedding, as compared with a placebo-treated group. The ribavirin aerosol therapy was well tolerated, with no adverse reactions or signs of toxicity in any of the volunteers. These results suggested that such therapy might be further explored in infants with lower-respiratory-tract disease due to RSV. Hence, we initiated a controlled, double-blind study of ribavirin aerosol therapy for such infection in infants admitted during the winters of 1982 and 1983.

METHODS

Patients

Infants enrolled in the study were chosen from those admitted to the infant ward or pediatric intensive-care unit with lower-respiratory-tract infection proved to be caused by RSV by immunofluorescent-antibody testing and subsequently by viral isolation. Only infants deemed ill enough to require at least three days of hospitalization were considered. Infants with underlying diseases such as congenital heart disease were excluded. Prematurity, however, did not constitute a reason for exclusion. The families and physicians of each infant were informed of the purpose, procedures, possible risks, and discomforts associated with the study, and the parents gave written informed consent for treatment with the experimental drug — i.e., ribavirin or placebo.

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Drug Administration and Study Design

The infants were assigned by use of a random table in double-blind manner to receive either drug or placebo (water). The drug in liquid form and as an aerosol is colorless and indistinguishable from water. Ribavirin or placebo was administered continuously except during a period of one to three hours in the morning before the time when the daily nasal wash specimen was obtained. The only other times the infant was away from the aerosol were during nursing or medical procedures that required removal of the infant. The aerosol was administered for a minimum of three days. The small-particle aerosol of the drug or placebo was produced by equipment developed by Knight and co-workers[6,17] (Viratek Corp., Covina, Calif.). The method employs a Collison generator to produce particles about 1.3 μm in diameter, which are administered at a rate of 12.5 liters per minute into an infant oxygen hood, oxygen tent, or inhalation tubing of a respirator. The concentration of ribavirin in the liquid reservoir was 20 mg per milliliter. The exact dosage of ribavirin delivered to an infant cannot be determined, since small-particle deposition in infants has not been measured. However, in adults treated with the same concentration of ribavirin administered by the same equipment, the dosage was determined to be 0.82 mg per kilogram of body weight per hour.[7]

Virology

On admission nasal-wash specimens and nasal swabs were obtained from each infant. The swab specimen was examined at the time of admission for RSV antigen by the indirect-immunofluorescence technique. The nasal wash was immediately inoculated onto HEp-2, cynomolgus kidney, canine kidney (MDCK), and fibroblastic cell lines for viral isolation. A nasal-wash specimen was obtained at the time of enrollment in the study and before the initiation of therapy, as well as on each subsequent day of the study, to measure the amount of RSV. The specimen (0.2 ml) was inoculated onto the HEp-2 cell line and titered in duplicate by serial 10-fold dilutions. All cultures were incubated at 35°C on roller drums and checked daily for typical cytopathic effect.

Clinical Evaluations

At the time of admission each infant was examined, and a complete history was obtained from the parents. At the time of enrollment and then throughout the study each infant was examined by one physician who was unaware of whether the infant was receiving

drug or placebo. The handling of the drug, placebo, and the aerosol-generating machines was performed by a different investigator who was never involved in the clinical evaluations. The families of the patients and the ward staff were also unaware of which therapy was being administered. The history, clinical signs, and symptoms were all recorded on standard forms. The daily signs and symptoms, which included vital signs, as well as lethargy, irritability, and poor feeding, were rated on computerized sheets from 0 (normal) to 3+ (severe). In addition, the child's general status — i.e., the severity of illness — was evaluated daily by use of a visual scale ranging from 0 (normal) to 4+ (most severe). The mark on this scale represented the examiner's overall assessment of the improvement or worsening that occurred each day.

Determination of Arterial Oxygen Saturation

Arterial oxygen saturation was determined at least once daily by ear oximetry. Arterial blood-gas levels were also determined in most infants, as deemed necessary for clinical management.

Assay of Sensitivity of Isolates to Ribavirin

To determine the relative sensitivity of the RSV strains isolated from different infants and to detect whether resistance might develop during therapy, isolates obtained before and after therapy — or the last isolate if shedding had ceased before the completion of therapy — were tested in a plaque-reduction assay against various concentrations of ribavirin as previously described .[15] Harvests of the nasal-wash isolates were inoculated in serial 10-fold dilutions onto HEp-2 cells in tissue-culture plates. After one hour of adsorption the cells were overlaid with a 0.6 per cent agarose medium containing no ribavirin or ribavirin at various concentrations (4, 8, 16, and 32 μg per milliliter). When the control plaque assay (without ribavirin) showed optimal plaque development, all assays were terminated by fixation and staining, and the plaques were counted. The per cent inhibition was calculated as follows: (virus titer without ribavirin − virus titer with ribavirin)/virus titer without ribavirin ×100.

Assays to Detect Presence of Ribavirin in Nasal Washes

Nasal-wash specimens were obtained for viral isolation and quantitation after the infant's aerosol therapy had been interrupted for periods of one to three hours. To be sure that ribavirin was not still present in the secretions and interfering with viral growth, specimens from four patients were tested in the same system used for viral titration. Nasal-wash specimens were heated at 65°C for 30 minutes to inactivate any virus present. To these specimens 10^3 $TCID_{50}$ of RSV (Long strain) was added, and titrations were performed by serial dilutions of these samples onto HEp-2 cells. The titers of these samples were comparable to the control titrations, indicating no inhibition of viral growth by the presence of ribavirin in the nasal washes.

Table 1. Characteristics of the Study Groups.

	Placebo Group	Ribavirin Group
No. of patients	17	16
Sex (M:F)	8:9	13:3
Age (wk)		
Median	10	13 *
Range	1–48	2–106
Days of illness before admission		
Mean	3.2	2.9 *
Range	1–7	1–5
Days from admission to start of therapy		
Mean	1.4	1.6 *
Range	1–5	1–3

*No significant difference between the groups (Mann–Whitney U test or Student's t-test).

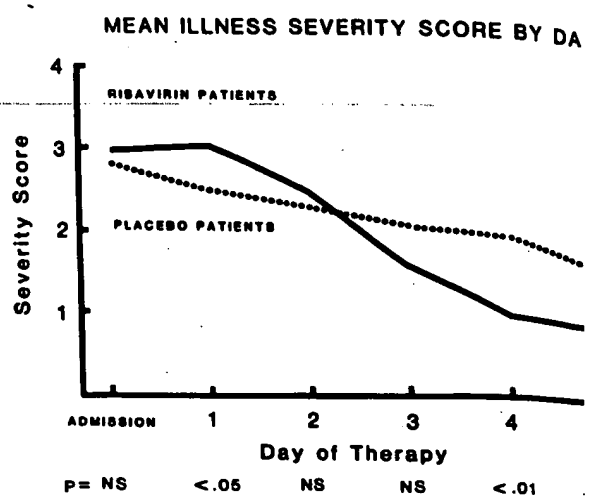


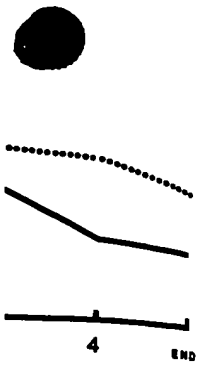
Figure 1. Means of Daily Scores for Severity of Illness
A score of 0 is normal, and 4 is most severe. Therapy ended average of 4.7 days in the placebo group and at 4.9 days ribavirin group, with ranges of 3 to 6 days. P values were mined by the Mann–Whitney U test and Student's t-tes

Results

Thirty-three infants with proved lower-respira tract disease from RSV were studied. All these in had RSV pneumonia, confirmed by chest roent grams, with or without bronchiolitis. Seventee fants were randomized to receive placebo, and ceived ribavirin. An additional six infants, who not included in the analysis, had life-threatening infection and were deliberately treated with rib as compassionate cases. The characteristics of t randomized infants are shown in Table 1.

Aerosol treatment was administered to the ran ized patients for an average of 20 hours per day f 6 days, for an average of 4.9 days in the rib group and 4.7 days in the placebo group. On a sion the severity of illness of the infants in the pl group was not significantly different from that infants in the ribavirin group (Fig. 1). Howev the time therapy was initiated (an average of 1. after admission) the infants in the placebo grou improved so that their illness score was signifi lower than that of the ribavirin group. Nevert the subsequent improvement after the first day apy was greater in the group treated with rib and their illness-severity score by the fourth therapy was significantly lower (Fig. 1). Furthe the mean increment of improvement in the score between Day 1 and the end of therap greater in the infants receiving ribavirin (0.7, P<0.01 by Mann–Whitney U test and St t-test). The changes in the severity of the variou of illness at the beginning and end of therapy f group are shown in Table 2. The change or d improvement in the lower-respiratory-tract si cept for wheezing, was significantly greater in t virin-treated group, whereas the change in t ture and upper-respiratory-tract signs w

SCORE BY DAY



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significantly different between the two groups. However, 51 per cent of all the infants were afebrile at the start of therapy. Seven infants in the ribavirin group and 9 in the placebo group had a temperature of 38°C or above on Day 1. By Day 4, all infants in the ribavirin group were afebrile, whereas two in the placebo group remained febrile.

The initial determination of the arterial oxygen saturation or blood-gas levels revealed that all the infants were hypoxemic, with oxygen saturation levels less than 92 per cent or partial arterial oxygen tension less than 62 mm Hg on breathing of room air (Fig. 2). All the infants received supplemental oxygen. However, these measurements were made in room air at the start and end of therapy in all but three infants, who were not included in the following analysis. The initial mean oxygen saturation and arterial oxygen tension in the two groups were not significantly different (oxygen tension in the ribavirin group was 49.4 mm Hg, as compared with 52 mm Hg in the placebo group). By the end of therapy the ribavirin-treated infants had significant improvement (mean oxygen tension, 62.4 mm Hg, $P<0.01$ by Wilcoxon signed rank test and paired t-test); the improvement in the placebo group was significant but less (56 mm Hg, $P<0.05$). The increment of improvement from the start to the end of therapy in the ribavirin group was an average of 13 mm Hg, as compared with 4 mm Hg in the placebo group ($P<0.001$ by Mann–Whitney U test).

The average and range of titers of RSV in the nasal washes were similar in both groups of infants before therapy (Table 3). By the end of treatment, however, the quantity of virus in the nasal washes of the ribavirin group was significantly less. The average number of days of RSV shedding from the start of therapy was 4.3 days in the placebo group and 2.9 days in the ribavirin group ($P<0.003$ by Student's t-test and the Mann–Whitney U test).

Two infants who had ceased shedding the virus at the end of treatment with ribavirin had a nasal-wash specimen three and four days later that showed the presence of RSV by indirect immunofluorescence, but

Table 2. Mean Severity Score for Sign or Symptom at Start and End of Treatment.

	Ribavirin Group		Placebo Group		P Value * for Change in Score
	START	END	START	END	
Temperature (°C)	37.9	37.2	37.9	37.4	NS
Nasal congestion and discharge	1.8	0.6	2.2	1.0	NS
Cough	2.3	0.9	1.8	1.6	<0.01
Rales	2.2	0.5	1.6	1.4	<0.01
Wheezing	1.1	0.2	1.3	0.8	NS
Retractions	2.2	0.2	1.5	1.0	<0.01
Lethargy	2.3	0.2	2.0	1.2	<0.01

*P value for unit change in score from start to end of therapy for placebo group versus ribavirin group (Mann–Whitney U test and non-paired t-test). NS denotes not significant.

BLOOD GASES AT START AND END OF THERAPY

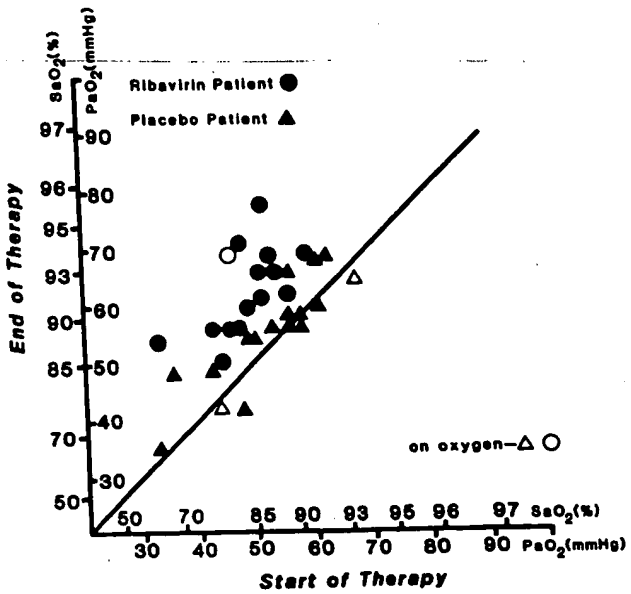

Figure 2. Arterial Blood-Gas Levels at the Beginning and End of Therapy with Ribavirin (●) or Placebo (▲).

The diagonal represents the line of identity — i.e., no change in values over the course of the therapy. SaO_2 denotes arterial oxygen saturation, and PaO_2 arterial oxygen tension. All infants were breathing room air, except those three indicated by open symbols.

no virus was isolated in tissue culture. In one of these infants the positive nasal wash was associated with clinical relapse. The last nasal washes obtained while these infants were being treated were tested for the presence of ribavirin, to be sure that the cessation of shedding was not due to inhibition of viral growth in tissue culture. The washes, however, were shown to contain no inhibitor of viral growth.

The sensitivity to ribavirin of the virus isolates in the nasal washes of both groups of patients obtained before and after treatment or, if shedding had ceased, from the last positive nasal wash was compared (Fig. 3). The mean per cent inhibition of all isolates was 65.4 per cent at a ribavirin concentration of 4 μg per milliliter, 91 per cent at 8 μg per milliliter, and 98 to 99.9 per cent at 16 μg per milliliter. At each concentration of ribavirin the mean per cent inhibition was not significantly different between first and post-treatment isolates in both groups of patients. Similarly, the sensitivity to ribavirin of the first and last isolates from any one patient did not differ appreciably, indicating that the virus did not become more resistant to the drug over the course of treatment.

The six children who were treated with ribavirin as compassionate cases had severe pneumonia fr RSV, for which three required prolonged assiste tilation. They received the aerosolized ribavi to 22 days. Five of these children recovered. ding of the virus from their tracheal secre had been present for 5 to 10 days or mor apy, ceased within 6 days of the start

Table 3. Titers of Respiratory Syncytial Virus in Nasal-Wash Isolates.

Group (No.)	Titer ($\log_{10}$ $TCID_{50}$/ml)		
	Before Treatment	At Day 3	At End of Treatment
Ribavirin (12)			
Mean	2.1 *	1.2 *	0.3 †
Range	0.4–5.7	0–4.2	0–1.7
Placebo (13)			
Mean	3.0	2.1	1.3
Range	0.4–5.9	0–4.2	0–4.2

*Not significantly different from value for placebo group.

†Significantly different from value for placebo group ($P<0.03$ by Mann–Whitney U test and Student's t-test).

treatment. The sixth infant, an 18-month-old with previously undiagnosed severe combined-immunodeficiency disease, had RSV and *Pneumocystis carinii* pneumonia and died after one month. Shedding of the virus was last documented on lung biopsy after 6 days of ribavirin treatment and 17 days before death.

No toxicity or side effects from the aerosol therapy were noted in any infant, including the compassionate cases in whom therapy was prolonged. Complete blood-cell counts obtained before, during, and at the end of therapy were not significantly different between the placebo and ribavirin groups, and no hematologic abnormality was noted. The randomized infants all recovered from their RSV infection. All 16 infants hospitalized during 1982 had follow-up examinations three to nine months after discharge. In the 14 of these infants in whom the arterial oxygen saturation was determined, values were all 93 per cent or higher, and the mean did not differ significantly between those who had received drug and those given placebo. Three of the eight infants receiving placebo in 1982 had one or more episodes of subsequent lower-respiratory-tract disease during the year after discharge, as did one of the eight infants who had received ribavirin.

Discussion

These findings indicate that infants with lower-respiratory-tract infection from RSV who are treated with ribavirin aerosol had significant improvement in lower-respiratory-tract signs, as compared with infants receiving placebo. This improvement in clinical status was associated with better levels of arterial oxygen saturation and diminished viral shedding.

The course of the upper-respiratory-tract signs was not significantly different between treated and placebo patients. This finding may be related to the difficulty in assessing the severity of such signs as nasal congestion and pharyngitis in young infants, or to the greater deposition of the small-particle aerosol in the lung parenchyma than in the upper respiratory tract.

The aerosol therapy appeared safe and was easily administered with the same equipment used to deliver oxygen or mist to the infant. Ribavirin aerosol has not produced any adverse effect in pulmonary function in treated adults in whom lung volumes and forced f rates were measured before and after carbachol c lenge.[8] That the aerosol treatment in infants did elicit airway hyperreactivity or other abnormalitie suggested by their improved blood-gas levels, the o feasible test of pulmonary function in these infa The general lack of side effects from this therapy, e in the compassionate cases treated for prolonged riods, suggests that in the severely ill infant thera might be continued beyond six days. In addition, possible relapse of one patient suggests that lon treatment may be necessary in some cases.

A concurrently conducted study in Houston si larly evaluated ribavirin aerosol in the treatment RSV infection in infants.[18] In contrast to our patien all 26 patients in that study had bronchiolitis and o four had any infiltrate evident on chest roentge grams. Aerosol treatment was administered for hours each day, whereas therapy in our study almost continuous. Nevertheless, clinical impro ment occurred significantly more rapidly in the infa in that study,[18] and no side effects or toxicity occurr

Transient side effects have been observed when bavirin has been administered by mouth. With doses of 1200 mg per day for two weeks, depressio the red-cell count has occurred, and transient i elevations in the serum bilirubin have been noted w

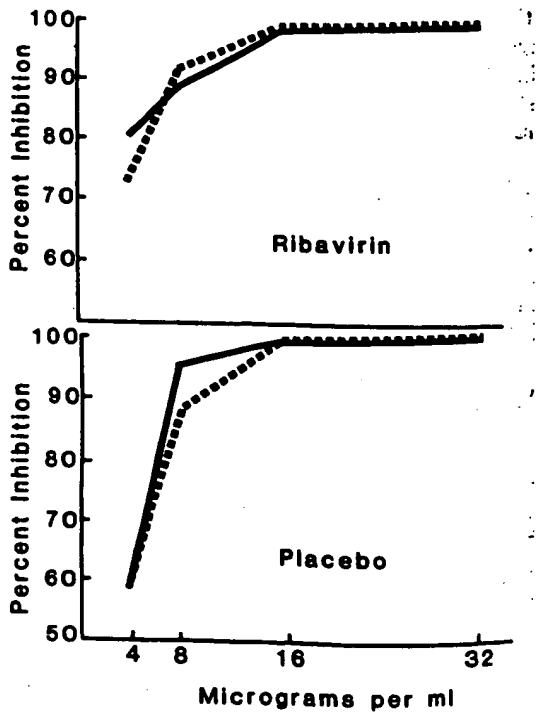

Figure 3. Mean per Cent Inhibition of Control Plaques of Res tory Syncytial Virus at Increasing Concentrations of Ribaviri First (Pretreatment) Nasal-Wash Isolate, (—), as Compared Last Isolates (.....).

The similarity of the curves indicates that treatment with the virin aerosol did not result in any increased resistance of the to the drug.

doses of 600 to 1000 mg per day for 5 to 10 days.[12,14,19,20] These changes were reversed by discontinuation of treatment. No such side effects have been noted with aerosolized ribavirin.[6-8,18] Teratologic effects of ribavirin have been noted in rabbits and rats but not in baboons.[21]

A chemotherapeutic agent might have particular appeal in RSV infection, since an effective vaccine has not been developed. Furthermore, such a vaccine would have to be administered during the neonatal period and elicit immunity superior to that produced by natural RSV infection, since reinfections may occur within a year or less.[4,5,22] Ribavirin therapy, on the other hand, is administered by aerosol over long periods, and is therefore appropriate at this time only for hospitalized infants. The number of infants requiring hospitalization for RSV infection is nevertheless appreciable. In long-term studies in Washington, D.C., infection with this virus accounted for 23 per cent of all hospital cases of acute respiratory-tract disease, and one of every 100 primary RSV infections resulted in a hospital admission.[2] In Tyneside, England, the rate of hospitalization for RSV infections is as high as 1 in every 50 infants in the first year of life.[23] Ribavirin therapy may be particularly beneficial for children at risk for severe and often fatal RSV infection, such as infants with congenital heart disease.[24]

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